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EXAMINER	
KWON, BRIAN YONG S	

ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 07/26/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/056,528	HOCHMAN, DARYL W.	
	Examiner	Art Unit	
	Brian S Kwon	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 January 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21,23-31,33 and 35-45* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21,23-31,33 and 35-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Summary of Action

I. The rejection of the claims 21, 23-26, 30-31, 33, 35-37 and 45 under 35 USC 112, first paragraph is maintained for the reason of the record.

II. The rejection of the claims 21-40 under 35 U.S.C.112, second paragraph, is not maintained in light of the amendment.

IV. The rejection of the claims 21, 23, 25-27, 30-31, 33 and 35-40 under 35 USC 102(b) as being anticipated by Read et al. (Cephalalgia, 1997, December, 17(8):826-832) is maintained for the reason of the record.

IV. The rejection of the claims 21, 23-24, 27-32 and 35-38 under 35 USC 102(b) as being anticipated by Mathew et al. (Neurology, 1996;46:1226-1230) is maintained for the reason of the record.

VI. Applicant's amendment necessitates a new ground of rejection(s) in this Office Action.

Status of Application

1. By an amendment filed January 27, 2004, claims 1-20, 22, 32 and 34 have been cancelled; claims 21, 23, 27, 28, 29-31, 35-38 have been amended; and claims 41-45 have been newly added. Claims 21, 23-31, 33 and 35-45 are currently pending for prosecution on the merits.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claim 21, 23-26, 30-31, 33, 35-37 and 45 are rejected under 35 USC 112, first paragraph, because the specification while being enabling for a treatment composition comprising furosemide or loop diuretic such as furosemide and furosemide-related compositions, does not reasonably provide enablement for the term "a treatment composition Na+K+2Cl- cotransporter antagonist activity to the central nervous system" (claims 21, 24-26, 33), "a loop diuretic" (claim 23), "Na+K+2Cl- chloride-dependent cotransporter antagonist inhibits Na+K+2Cl- cotransport in glial cells" (claim 30) or "Na+K+2Cl- chloride-dependent cotransporter antagonist exhibits a high degree of activity in glical cell populations and a lesser degree of activity in neuronal and renal cell populations" (claim 31), "Na+K+2Cl- chloride-dependent cotransporter antagonist that is effective in inhibiting synchronized neuronal population discharges in the CNS of a mammal without decreasing excitatory synaptic transmission" (claim 35), "antagonist blocks spontaneous synchronized depolarizing oscillations of neuronal population activity in the central nervous system" (claim 36), "Na+K+2Cl- chloride-dependent cotransporter antagonist produces modulation of the chloride concentration in extracellular space in the central nervous system" (claim 37) and "a cation chloride cotransporter antagonist to the central nervous system of the subject" (claim 45). The specification does not enable any person skilled in the art to which it pertains, or with

which it is most nearly connected, to use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01 (a)). These include: 1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. All the factors have been considered with regard to the claim, with the most relevant factors discussed below.

Nature of the Invention: All rejected claims are drawn to method of treating migraine headache, cortical spreading depression and other headache conditions and/or symptoms of such conditions in subjects with the administration of said compositions to the subject.

State of the Art: The art recognizes the treatment of migraine headache, cortical spreading depression and/or the treatment of migraine by controlling "visual aura" via administering furosemide.

Relative Skill of Those in the Art: The relative skill of those in pharmaceutical art is high.

Predictability of the Art: The unpredictability of the pharmaceutical art is very high. In fact, the courts have made a distinction between mechanical elements function the same in different circumstances, yielding predictable results, chemical and biological compounds often react unpredictably under different circumstances. Nationwide Chem.

Corp. v. Wright, 458 F. supp. 828, 839, 192 USPQ 95, 105(M.D. Fla. 1976); Aff'd 584 F.2d 714, 200 USPQ 257 (5th Cir. 1978); In re fischer, 427 F.2d 833, 839, 166 USPQ 10, 24(CCPA 1970). Thus, the physiological activity of a chemical or biological compound is considered to be an unpredictable art. Likewise, the physiological or pharmaceutical activity of preventing or treating migraine headache, cortical spreading depression and other headache conditions and/or symptoms of such conditions prior to filling of the instant invention was an unpredictable art.

Breadth of Claims: The claims are very broad due to the vast number of possible compounds of that are described as being "Na+K+2Cl- cotransporter antagonist activity to the central nervous system", "a loop diuretic", "Na+K+2Cl- chloride-dependent cotransporter antagonist inhibits Na+K+2Cl- cotransport in glial cells", "Na+K+2Cl-chloride-dependent cotransporter antagonist exhibits a high degree of activity in glial cell populations and a lesser degree of activity in neuronal and renal cell populations", "Na+K+2Cl- chloride-dependent cotransporter antagonist that is effective in inhibiting synchronized neuronal population discharges in the CNS of a mammal without decreasing excitatory synaptic transmission", "antagonist blocks spontaneous synchronized depolarizing oscillations of neuronal population activity in the central nervous system", "Na+K+2Cl- chloride-dependent cotransporter antagonist produces modulation of the chloride concentration in extracellular space in the central nervous system" and "a cation chloride cotransporter antagonist to the central nervous system of the subject" .

Guidance of the Specification:

In the instant case, given the unpredictability of the physiological or pharmaceutical activity of the claimed agent, the agent having "Na+K+2Cl- cotransporter antagonist activity to the central nervous system", "a loop diuretic", "Na+K+2Cl- chloride-dependent cotransporter antagonist inhibits Na+K+2Cl- cotransport in glial cells", "Na+K+2Cl- chloride-dependent cotransporter antagonist exhibits a high degree of activity in glial cell populations and a lesser degree of activity in neuronal and renal cell populations", "Na+K+2Cl- chloride-dependent cotransporter antagonist that is effective in inhibiting synchronized neuronal population discharges in the CNS of a mammal without decreasing excitatory synaptic transmission", "antagonist blocks spontaneous synchronized depolarizing oscillations of neuronal population activity in the central nervous system", "Na+K+2Cl- chloride-dependent cotransporter antagonist produces modulation of the chloride concentration in extracellular space in the central nervous system" and "a cation chloride cotransporter antagonist to the central nervous system of the subject" in treating migraine headache, cortical spreading depression and other headache conditions and symptoms of such conditions is insufficient for enablement. The specification provides no guidance, in the way of enablement for that claimed agent other than furosemide, more broadly loop diuretic such as furosemide and furosemide-related compositions. The specification fails to provide sufficient information or guidance that all compounds that are potentially suitable for the invention work similarly as to furosemide. Furthermore, numerous possible compounds that are suitable for the invention are not necessarily structurally related to each other, and the skill artisan would have not known that which compounds of the claimed

compounds are capable of accomplishing the desired result of the claimed invention without undue amount of experimentation.

In re Fisher, 427 F. 2d 833, 166 USPQ 18 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also In re Wright, 999 F.2d 1557, 27 USPQ2d 1510 (Fed. Cir. 1993); In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). This is because it is not obvious from the disclosure of one species, what other species will work. In re Dreschfiedl, 110 F. 2d 235, 45 USPQ 36 (CCPA 1940), vies this general rule: "it is well settled that in cases involving chemicals and chemical compounds, which differ radically in their properties it must appear in an applicant's specification either by the enumeration of a sufficient number of the members of a group or by other appropriate language, that the chemicals or chemical combination included in the claims are capable of accomplishing the desired result." The article "Broader than the Disclosure in Chemical Cases," 31 J.P.O.S.5, by Samuel S. Levin covers this subject in detail. A disclosure should contain representative examples, which provide reasonable assurance to one skilled in the art that the compounds fall within the scope of a claim will possess the alleged activity. See In re Riat et al. (CCPA 1964) 327 F2d 685, 140 USPQ 471; In re Barr et al. (CCPA 1971) 444 F 2d 349, 151 USPQ 724.

The Presence or Absence of Working Examples: As stated above, the instant specification only provides enabling disclosure for the activity of furosemide in inhibiting cortical spreading depression, treating migraine headache, and reducing "visual auras" of migraine (page 5, lines 1-25 of the instant specification).

The Amount of Experimentation Necessary: The quantity of experimentation needed to be performed by one skilled in the art is yet another factor involved in the determining

whether "undue experimentation" is required to make and use the instant invention. "the test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." In re Wands, 858 F.2d 737, 8 USPQ2d 1404 (citing In re Angstadt, 537 F.2d 489, 502-04, 190 USPQ 214, 218 (CCPA 1976)). For these reasons, one of ordinary skill in the art would be burdened with undue "painstaking experimentation study" to determine all of the agents having " Na+K+2Cl- cotransporter antagonist activity to the central nervous system", "a loop diuretic", "Na+K+2Cl- chloride-dependent cotransporter antagonist inhibits Na+K+2Cl- cotransport in glial cells", "Na+K+2Cl-chloride-dependent cotransporter antagonist exhibits a high degree of activity in glical cell populations and a lesser degree of activity in neuronal and renal cell populations", "Na+K+2Cl- chloride-dependent cotransporter antagonist that is effective in inhibiting synchronized neuronal population discharges in the CNS of a mammal without decreasing excitatory synaptic transmission", "antagonist blocks spontaneous synchronized depolarizing oscillations of neuronal population activity in the central nervous system", "Na+K+2Cl- chloride-dependent cotransporter antagonist produces modulation of the chloride concentration in extracellular space in the central nervous system" and "a cation chloride cotransporter antagonist to the central nervous system of the subject" that would be enabled in this specification.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

3. Claims 21, 23, 25-27, 30-31, 33 and 35-40 are rejected under 35 U.S.C. 102(b) as being anticipated by Read et al. (Cephalalgia, 1997, December, 17(8):826-832).

Read teaches the use of furosemide in saline solution, which is a loop diuretic with activity at the electroneutral Na+K+2CL-, in inhibiting regenerative cortical spreading depression in anaesthetized cats, wherein the mechanism of inhibition of cortical spreading depression activity by furosemide may be through alterations in cortical ion buffering capacity or inhibition of cell swelling in neurons or glia (abstract; page 826, column 1, para. 1-3 thru column 2, para. 1; page 837, column 2, para. 2).

Although Read is silent about the incorporation of "a blood brain barrier permeability enhancer" or hyperosmotic agent"; "exhibits a high degree of activity in glial cell popoulations and a lesser degree of activity in neuronal and renal cell populations"; "inhibiting the synchronization of neuronal population discharges in the CNS of a mammal without decreasing excitatory synaptic transmission"; "blocks spontaneous synchronized depolarizing oscillations of neuronal population activity in the central nervous system"; and "the treatment composition is formulated to facilitate crossing of the blood brain barrier", such characteristics or properties deems to be inherent to the referenced administration of furosemide in saline solution for inhibiting cortical spreading depression. Therefore, the reference anticipates the claimed invention.

8. Claims 21, 23-24, 27-32 and 35-38 are rejected under 35 U.S.C. 102(b) as being anticipated by Mathew et al. (Neurology, 1996;46:1226-1230).

Mathew the use of acetazolamide and furosemide in combination with abortive antimigraine agents (e.g., ergotamine, DHE, or sumatriptan) and prophylactic agents such as beta blockers, amitriptyline or methysergide for the treatment of chronic daily headache including migraine headache in human (abstract; page 1226, column 2, para. 5 thru page 1228, column 1, para. 1 ; page 1228, column 2, para. 6 thru page 1229, column 1, para. 1). The reference discloses that said combination resulted "in the number of days of severe headache, reduced consumption of abortive agents, and overall improvement of quality of life".

Although Mathew is silent about "exhibits a high degree of activity in glial cell populations and a lesser degree of activity in neuronal and renal cell populations"; "modulates the synchronization of neuronal discharges in the central nervous system"; "blocks spontaneous synchronized depolarizing oscillations of neuronal population activity in the central nervous system"; and "produces modulation of the chloride concentration in extracellular space in the central nervous system", such characteristics or properties deems to be inherent to the referenced administration of furosemide in saline solution for inhibiting cortical spreading depression. Therefore, the reference anticipates the claimed invention.

Since the scope of instantly claimed invention encompasses the combination therapy (either coadministration or separate administration), the referenced administration of the acetazolamide and furosemide in combination with the antimigraine

agents for the treatment of migraine headache by "reducing the number of days of severe headache...overall improvement of quality of life" anticipates the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

4. Claims 41-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Read et al. (Cephalalgia, 1997, December, 17(8):826-832) or Mathew et al. (Neurology, 1996;46:1226-1230).

The teaching of Read or Mathew has been discussed in above 35 USC 102(b) rejection.

Newly added claims now require the administration of said loop diuretic by intranasal or intracranial administration.

However, determination of such delivery dosage forms having optimum therapeutic index is well considered within the skill of the artisan, and the artisan would

be motivated to determine optimum delivery dosage forms to maximize the effects of drugs. Those of ordinary skill in the art would have readily optimized effective dosage forms as determined by good medical practice and the clinical condition of the individual patient. Determination of appropriate dosage forms involving each of the above mentioned formulations would have been apparent to those of ordinary skill in the art, and routinely made by those of ordinary skill in the art and be within the ability of tasks routinely performed by them without undue experimentation. One would have been motivated to combine these references and make the modification because they are drawn to same technical fields (constituted with same ingredients and share common utilities), and pertinent to the problem which applicant concerns about. MPEP 2141.01(a).

Response to Arguments

5. Applicant's arguments filed January 27, 2004 have been fully considered but they are not persuasive.

In response to the rejection of the claims under 35 USC 112, first paragraph, "scope of enablement rejection", applicant alleges that compounds that inhibit Na+K+2Cl- cotransporters are well known to those skilled in the art, and routinely determined by assays without undue experimentation. The examiner disagrees. Unlike applicant's allegation, the assays methods (described methods for screening candidate compounds for desired activities in US Patents 5902732, 5976825, 6096510 and 6319682) requires undue amount of experimentation to find suitable compounds and test for their utility of treating migraine headaches, cortical spreading depression and symptoms of such conditions. The skill artisan would have not known that which

compounds of the claimed compounds are capable of accomplishing the desired result of the claimed invention without undue amount of experimentation.

In response to the rejection of the claims under 35 U.S.C. 102(b) as being anticipated by Read et al., applicants states that this rejection is improperly lodged insofar as the references was not publicly available more than a year before the filing of applicant's US Provisional Application No. 60/113,620 on December 23, 1998, to which the subject application claims benefit of priority. Applicant alleges that the reference was not publicly available prior to January 6, 1998 (dated-stamped pages of the cited reference from Duke University Medical Library and from Thomas Jefferson University Library). This argument is considered unpersuasive. According to the information obtained by the examiner, Cephalalgia is published 8 issues/year excluding January, March, July and September, usually in the first week of month, and delivers to the subscriber. Although applicant provides the library receival date of the December issue of the article (January 6,1998), such showing cannot be considered as overcoming evidence for 35 USC 102(b) rejection since it is not same as the publication date. Therefore, considering the usual monthly publication date of the article, the communication between authors and editors (Received 28 May 1997, accepted 12 September 1997) and the absence of evidence to the contrary, the examiner maintains that Read anticipates the claimed invention.

Although applicant discusses the relevancy of Mathew's teaching in page 10, para. 2 of Remarks, however, no argument pointing out disagreements with the examiner's contentions is present. Since the referenced teaching of using composition

comprising acetazolamide and furosemide in combination with abortive antimigraine agents (e.g., ergotamine, DHE, or sumatriptan) and prophylactic agents such as beta blockers, amitriptyline or methysergide for the treatment of chronic daily headache including migraine headache in human "metes and bounds" the instantly claimed conditions, the examiner maintains that Mathew anticipates the claimed invention.

Conclusion

6. The applicant's amendment necessitated a new ground of rejection in this Office Action.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

7. No Claim is allowed.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Kwon whose telephone number is (571) 272-0581. The examiner can normally be reached Tuesday through Friday from 9:00 am to 7:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marianne Seidel, can be reached on (571) 273-0584. The fax number for this Group is (703) 872-9306.

Any inquiry of a general nature of relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

VICKIE KIM
PRIMARY EXAMINER

Brian Kwon
Patent Examiner
AU 1614